Epitomes

Important Advances in Psychiatry

Psychiatry

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The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association, and the summaries were prepared under the direction of Victor I. Reus, MD, and the panel.

Magnetic Resonance Spectroscopy and Psychiatry

WITH THE AVAILABILITY OF in vivo high-resolution magnetic resonance spectroscopy (MRS), it is now possible to study directly and noninvasively the chemistry and metabolism of human brain tissue. Magnetic resonance spectroscopy has tremendous potential for detecting specific neurobiologic abnormalities underlying the major psychiatric disorders. Because the procedure is done with the same magnet that is used for magnetic resonance imaging, there is an excellent opportunity to study regional brain structure and function simultaneously with both procedures.

Magnetic resonance spectroscopy can be used to study the resonance spectra of compounds in the brain that contain odd-numbered nuclei such as hydrogen 1, lithium 7, carbon 13, oxygen 17, fluorine 19, sodium 23, magnesium 25, and phosphorus 31. Because the technology uses magnetism and radio waves rather than ionizing radiation or radioactive tracers, it is considered safer than positron-emission tomography (PET) or single-photon-emission computed tomography (SPECT). The relative cost of an MRS study is comparable to a SPECT study and less expensive than a PET study. In addition, because MRS can be safely repeated numerous times, it is an ideal technique for assessing longitudinal changes in brain metabolism. Studies using ^{31}P, for example, yield information about high-energy phosphate compounds such as adenosine triphosphate and phosphocreatine, as well as phospholipid metabolism (phosphomonoesters and phosphodiesters). If proton spectra are obtained, information about psychiatrically relevant compounds such as lactate, glutamate, aspartate, γ-aminobutyric acid (GABA), creatine, choline, and *N*-acetylaspartate (a putative neuronal marker) can be obtained from any specific brain region. Such a window into the chemistry of the living brain of patients with psychiatric disorders is clearly unprecedented. These characteristics are why MRS studies of the brain have been referred to as "noninvasive biopsies" of brain tissue.

Recent MRS investigations of psychiatric disorders such as schizophrenia and bipolar disorder using ^{31}P have yielded results suggesting alterations in both brain high-energy phosphate and membrane phospholipid metabolism in the frontal and temporal lobes. In some studies, these alterations have been associated with the severity of clinical symptoms. Proton (^{1}H) MRS studies in schizophrenia, bipolar disorder, and depression have also yielded valuable information regarding changes in metabolites such as *N*-acetylaspartate, choline, and creatine. The changes in *N*-acetylaspartate are particularly noteworthy because they suggest decreases in the neuronal density of certain brain regions. Some studies have also documented alterations in glutamate, aspartate, and GABA levels in the frontal brain regions of patients with schizophrenia. Magnetic resonance spectroscopic investigations in patients with autism and various forms of dementia using ^{1}H and ^{31}P have also elicited interesting findings.

Finally, in vivo ^{1}H, ^{7}Li, ^{13}C, ^{19}F, or ^{31}P MRS can be used for pharmacologic studies of the human brain either through the direct measurement of drug concentrations or of drug effects on brain metabolism. Perhaps most exciting for psychiatry is that MRS using ^{19}F has measured the human brain concentrations of fluorinated psychoactive drugs such as fluphenazine, trifluoperazine, and fluoxetine. In a similar manner, MRS using ^{7}Li and ^{31}P has measured the human brain concentrations of lithium and demonstrated effects of lithium on phospholipid metabolism.

It is clear that as the field of in vivo MRS develops, it will contribute to major advances in identifying neurobiologic abnormalities in psychiatric disorders that are perhaps too subtle to detect by other methods. It is hoped that this technology will also help to facilitate the monitoring and metabolic effects of pharmacologic and other treatment modalities in these disorders. At present, it has not been determined how MRS studies will be used in the clinical setting.

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Risperidone—A New Antipsychotic Agent

RISPERIDONE is the first antipsychotic agent designed to antagonize both dopamine and serotonin receptors as does clozapine. Unlike clozapine, it has little effect on cholinergic and β-adrenergic receptors but does affect α_2-adrenergic and histamine H_1 receptors.

In a series of controlled studies, risperidone has been shown to be an active antipsychotic agent in doses ranging from 4 to 16 mg. Dosages greater than 6 mg have not shown greater activity, but have more side effects, including extrapyramidal signs. The use of a dose of 6 mg was shown to be superior to both a placebo and 20 mg of haloperidol and with no difference in extrapyramidal effects compared with the placebo. Thus, at this dosage, a beneficial effect was seen in both "positive" (such as delusions and hallucinations) and "negative" (such as emotional withdrawal and blunted affect) symptoms with a minimum of extrapyramidal signs. This led to the suggestion of the rapid titration of this dosage for everyone, but clinical experience has shown this to be a mistake. First (and apart from its cost), not all patients require 6 mg. Second, although there was no group difference between the use of 6 mg and a placebo, extrapyramidal signs do develop in some persons at this dosage, with dystonic reactions reported at dosages as low as 2 mg. It appears now that risperidone is probably twice as potent as haloperidol; therefore, maintenance dosages will generally range from 1 mg upwards, with individual dose titration as necessary. Many patients do well at 3 or 4 mg per day, and the use of 4 mg has been shown to be therapeutic in a European controlled trial. For older patients, even smaller dosages have been shown to be effective. Specific controlled studies in these patients have not yet been reported in the literature, but clinical reports of the use of doses lower than 1 mg being effective have led the manufacturer to try producing tablets smaller than 1 mg and a liquid preparation as well.

Risperidone has a half-life of 3 to 20 hours and is extensively metabolized to an active agent, 9-hydroxyrisperidone, which has a half-life of 21 to 30 hours. This metabolism takes place in the liver through the cytochrome P-450 IID6 isoenzyme system. This enzyme system is responsible for the metabolism of many neuroleptic and antidepressant agents, creating the possibility of important drug interactions. Isomorphism of this enzyme activity may explain the individual differences in metabolism. The majority of the drug's activity derives from the 9-hydroxy metabolite; yet, despite the long half-life of this metabolite, twice-a-day dosing is recommended by the manufacturer. This is apparently a Food and Drug Administration requirement despite the lack of any studies of once-a-day dosing. Drugs such as thioridazine, haloperidol, and loxapine are frequently used once a day at bedtime in routine clinical practice despite the lack of studies of once-a-day dosage. For the treatment of psychotic states, a starting dose of 1 mg twice a day should be used and the dosage increased slowly as the clinical state dictates, similar to the use of other antipsychotic agents. Converting from a typical neuroleptic to risperidone should not be done abruptly. It is also important not to discontinue anticholinergic drugs abruptly because this may lead to a worsening of extrapyramidal signs. If a patient is taking anticholinergic drugs, these should be continued and later withdrawn slowly after the transition to risperidone has taken place. Side effects with the use of risperidone include dizziness, sleepiness, and nausea, which, like extrapyramidal effects, are probably dose-related. Tachycardia and weight gain have also been reported.

Risperidone is expensive, costing as much as $2,000 per year per patient, but it offers an advantage over conventional neuroleptic agents in some patients, with about a 15% better response rate. It represents a distinct advance in therapeutics, particularly because it does not require blood monitoring, as does the use of clozapine. The exact place of risperidone in therapeutics is still to be determined. Many psychopharmacologists think that it should be a treatment of first choice in schizophrenia. Others suggest that patients should have an adequate trial of at least one typical neuroleptic agent, such as chlorpromazine or haloperidol, and if nonresponsive to this, then risperidone would be the next choice. The place of risperidone in the treatment of older patients or in affective disorders and other conditions where antipsychotic agents are used remains to be determined.

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Managing Agitated Patients in a General Hospital

AN AGITATED PATIENT in a general hospital setting is disruptive, dangerous, and usually in delirium. Agitated patients cause delays in patient recovery, increase patient and hospital costs, heighten family and staff anxiety, and can lead to patient and staff injury. Severely agitated patients show excessive physical activity and present a serious risk to themselves. Delirium is the most frequent cause of severe agitation in a general hospital, though mania, psychosis, dementia, and severe anxiety or depression can sometimes present with substantial agitation.